BCG scar formation and test results in two generations

Article *in* Shiraz E Medical Journal · January 2011

CITATION
1

READS
36

4 authors, including:

Abbas Allami
Qazvin University of Medical Sciences
30 PUBLICATIONS **67** CITATIONS
SEE PROFILE

Navid Mohammadi
Qazvin University of Medical Sciences, Iran University of Medical Sciences
49 PUBLICATIONS **154** CITATIONS
SEE PROFILE

Ali Lashgari
Shahid Beheshti University of Medical Sciences
6 PUBLICATIONS **4** CITATIONS
SEE PROFILE

In the name of God

Shiraz E-Medical Journal
Vol. 12, No. 1, January 2011

http://semj.sums.ac.ir/vol12/jan2011/89036.htm

BCG Scar Formation and Test Results in Two Generations.

Allami A*, Mohammadi N**, Afaghi A±, Lashgari A∞.

*Assistant Professor, Department of Infectious Disease, Qazvin University of Medical Science, Qazvin, Iran, **Assistant Professor, Department of Community Medicine and Health, Iran University of Medical Science, Tehran, Iran,± Assistant Professor, Department of Community Medicine and Health, Qazvin University of Medical Science, Qazvin, Iran, ∞General Practitioner.

Correspondence: Dr. Abbas Allami, Department of Infectious Disease, Qazvin University of Medical Science, Qazvin, Iran, Telephone: +98(281) 3360-904, Fax: +98(281) 3360-904, Email: allami@qums.ac.ir.

Received for Publication: October 2, 2010, Accepted for Publication: November 7, 2010.

Abstract:

Introduction: Considering that BCG injection in newborns is part of TB control program in Iran many years ago, we aimed to compare prevalence of childhood BCG vaccination scar with previous study and asses influence of household crowding on TST result.
Aims: Considering that over time there is likely to reduce the immune response, two groups of subjects were selected among young and middle aged.
Methods and Material: This cross sectional study was conducted in Zia Abad of Qazvin (a province of Iran) during year 2008. 261 participants randomly were selected (139 asymptomatic children (12-16 y) and 122 adults (40-50 y)). A questionnaire was used to obtain prior histories of BCG vaccination, known exposure to tuberculosis, prior acquired of TB, symptoms of TB disease and household crowding. BCG vaccine scar was ascertained and all participants were tested with 5TU-PPD. Reactions of 10 mm or more were considered positive.
Statistical analysis used: Using student t test, chi square and Fisher's exact test, the collected data was analyzed.
Results: BCG scar was observed in 78.4% of participant (91.4% children vs. 78.6% adults) which the difference was significant. Twenty three (16.5%) of children and 24 (19.7%) of adults had tuberculin reactivity of ≥10 mm. In children and parent groups, positivity of TST had significant direct association with presence of BCG scar and crowding.
Conclusions: Most vaccinated children had a scar. Our results demonstrate that a TST applied after BCG vaccination usually produces a reaction of <10 mm. In addition, there is a significant relationship between the tuberculin reactivity and both presence of BCG scar and crowding among children and adult groups.

Keywords: Tuberculin Test, Scar, Crowding, Tuberculosis

Introduction:

Tuberculosis (TB) remains a major cause of illness and death worldwide, especially in Asia and Africa. An estimated 9.27 million incident cases of tuberculosis occurred in 2007.[1, 2]

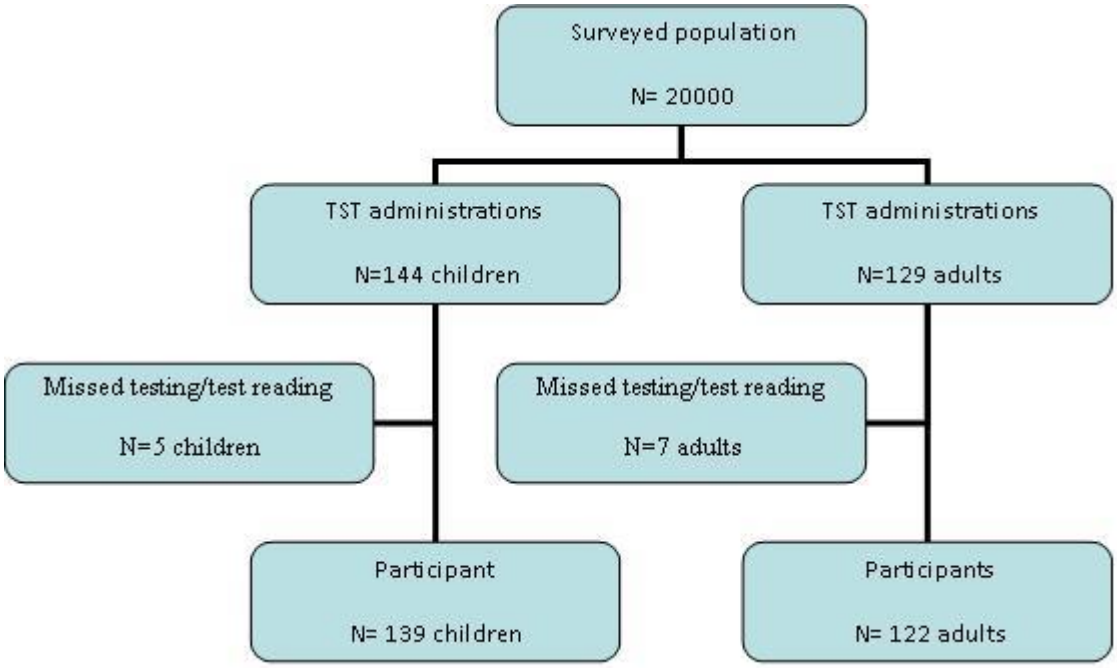
Accurate determination of the prevalence of latent infection is essential for understanding of the epidemiology of tuberculosis, designing, and evaluation of tuberculosis control strategies and equally, from a population perspective, estimating the prevalence of LTBI is important for evaluating the performance of health policies and interventions.[3] Tuberculin skin test (TST) is known as a means of determining tuberculous infection prevalence rate and still is the only routinely available and comparatively cheap method of detecting individuals infected with Mycobacterium tuberculosis.[4] The absence or presence of a scar is used as an indicator of previous BCG vaccination in clinical settings as well as surveys performed by health institutions such as the Expanded Program on Immunization to assess vaccine uptake.[5] However, the sensitivity of the BCG scar as an index of vaccination status is still the subject of controversy.[6]

Considering that BCG injection in newborns is part of TB control program in Iran many years ago[7], we aimed to compare prevalence childhood BCG vaccination scar with previous study and asses influence of household crowding on TST result. Also we decided to study the pattern of the reaction at different generations after BCG vaccination, hence two groups of subjects were selected among young and middle aged

Subjects and Methods:

This cross sectional study was conducted in Zia Abad, a town with an estimated population of 22000 in 60 km southwest of Qazvin (province in the northern of Iran) during year 2008. In order to determine the prevalence of TST positivity in the past and present, we chose 261 participants in two groups of adults and children. Sample size calculation was based on estimation of proportion in a population, with a type one error equal .05, p=0.1 for children and p=.09 for parents groups. In the first step, 144 asymptomatic children randomly selected from students of grades 6 to 9 (12-16 y). In the second step, 129 adults (40-50 y) randomly selected from the children's parents. Subjects who refused for conducting TST, or were "missed testing/test reading" were excluded. In addition, participants with clinical sign and symptom of tuberculosis, atopic dermatitis, extensive burn, recent surgery, gross medical condition, receiving immunosuppressive drugs, and recent skin eruptions with fever were excluded.[8] Finally, 139 children (57% M, 43% F) and 122 adults (44% M, 56% F) were studied (Fig 1).

Figure 1: Flow diagram of the study population



The study was approved by the Human Research Ethics Committee of Qazvin University of Medical Science and an informed consent form was obtained from each participant. A questionnaire was used to obtained prior histories of BCG vaccination, known exposure to tuberculosis, prior acquired of TB, symptoms of TB disease and household crowding. We explored the latter in several questions by asking about number of living room, family size, living area space (m2) and family density (m2/person). These indicators were based on a similar study (Baker M et al).[9] Questionnaires were completed by one bilingual interviewer because Turkish is second popular language in that area. Tuberculin testers were selected from the health care workers who were trained according to standard guidelines.[10] After interviewing the subjects, BCG vaccine scar was ascertained by inspection of the left deltoid region. All participants were tested with 0.1 ml 5TU-PPD (5 tuberculin units of purified protein derivative; Razi institute, Tehran, Iran). PPD injected intradermally on the volar aspect of the left forearm. Over the study, all tuberculin solutions were stored in vaccine carrier in 2-6 ◦C. The tests were read after approximately 72 hours. For each participant, the maximum transverse diameter of indurations (not erythema) was measured with a ruler by pen-rolled method. All reactions of 10 mm or more were considered positive. Those with a positive TST were evaluated for active TB by clinical examination. Statistical analysis was performed using OpenEpi (version 2.3; OpenEpi, Atlanta, GA, USA). Mean±SE (standard error) were calculated to describe quantitative variables (prevalence ratios).[11] Chi-square test (fisher's exact where neces-

sary) were used to compare qualitative variables (factors associated with positivity of TST) and Student's t-test was used to compare quantitative variables between the two groups (children and parent groups). P-values less than 0.05 were considered significant.

Due to not observing significant association between both sex and age with the prevalence of TST posivity, the Post hoc power analysis of the data was performed.

Results:

Overall, BCG scar was observed in 223/261(85.4%) of participant with 91.4% (CI 95: 85.7%-95.2%) children vs. 78.7% (CI 95: 70.76%-85.27%) adults which the difference was significant (Difference = 12.8% [CI 95: 4.2% - 21.4%]). This study showed that 23 (16.5%) of children and 24 (19.7%) of adults had tuberculin reactivity of ≥10 mm which the difference between two groups was not significant (table 1) (Difference = -3.2% [CI 95: -12.6% – 6.2%]).

Distribution of variables in the study (sex, TST result, presence of BCG scar, income, and crowding indicators) in children and adult participants has been showed in table 2. In children, positivity of TST had significant direct association with presence of BCG scar, large family size (respectively p= 0.043, 0.019) and inverse association with living area space, number of living room, and family density (m2/person) (respectively p= 0.001, 0.008, <0.001). In adult group positivity of TST had significant direct association with presence of BCG scar, large family size (p= 0.033) and inverse association with living area space, number of living room, and family density (m2/person) (respectively p= 0.008, 0.001, 0.044).

To find out association between both sex and age with TST positivity, we used the TST Posivity frequencies of 0.20 (Male), 0.16 (Female), 0.16 (children), 0.20 (adult) and considering a P value of .05 the detected powers were 0.16 and 0.10 respectively.

Table 1: Result of PPD test in children and parent's groups.

Group	Test PPD			Total
	Negative	suspected	Positive	
Children	79(56.8%)	37(26.6%)	23(16.5%)	139(100%)
Parent	62(50.8%)	36(29.5%)	24(19.7%)	122(100%)
Total	141(54%)	73(28%)	47(18%)	261(100%)

0-4: Negative, 5-9: suspected, ≥10: Positive

Table 2: Frequency distribution of variables and TST results of two groups

	Children			Parent			Total		
Tuberculin reactivity (mm) Factor	**0-9***	**≥10^**	**Total**	**0–9**	**≥10**	**Total**	**0-9**	**≥10**	**Total**
Sex									
Female	52	8	60	56	12	68	108	20	128
Male	64	15	79	42	12	54	106	27	133
BCG scar									
Negative	12	0	12	24	2	26	36	2	38
Positive	104	23	127	74	22	96	178	45	223
Living area space (m2)									
< 70	26	15	41	21	14	35	47	29	76
70-100	59	6	65	51	5	56	110	11	121
>100	31	2	33	26	5	31	57	9	66
Living room (N)									
1	10	8	18	7	10	17	17	18	35
2	65	13	78	56	12	68	121	25	146
≥3	41	2	43	35	2	37	76	4	80
Family size (N)									
≤ 5	85	10	95	69	12	81	154	22	176
> 5	31	13	44	29	12	41	60	25	85
Family density π									
< 15	30	18	48	29	13	42	59	31	90
15-30	55	3	58	41	10	51	96	13	109
> 30	31	2	33	28	1	29	59	3	62
Income ($)									
<300	16	2	18	71	16	87	87	18	105
300-400	75	18	93	23	5	28	98	23	121
>400	25	3	28	31	3	34	56	6	62

TST: Tuberculin Skin Test; BCG: Bacillus Calmette–Guérin, *: Negative or suspected, ^: Positive, π: (m2/person)

Discussion:

This study showed that most vaccinated children (91.4%) had a scar, while in two similar Iranian studies conducted in 1991 and 1996; the reported figures were 27.2% and 71.5% respectively.[12] Comparison of results of these studies shows that the scar formation rate after BCG vaccination in Iran has increased. In our study, the BCG scar in children was a sensitive indicator of vaccination status whereas scar presence persisted 12-16 years after vaccination.

Failure to form a scar may be related to factors such as lack of maturation of the immune system[13], faulty technique or use of a nonpotent vaccine[14] and HLA class II high-risk allele.15 The differences between our study and previous findings could be attributed to the type of vaccine, and the method of vaccination. In studies that children were immunized soon after at birth, reported scar-failure rates is compatible with results of our study.[16-18] Most of the health authorities express that BCG vaccination should result in a long-standing scar in more than 90% of the cases.[19] When adolescents from these same communities with vaccination records were examined for BCG scar presence; a similar scar failure rate was found.

BCG scar was observed in 91.4% children vs. 78.7% adults, which the difference

was significant. No recorded history of BCG immunization in a number of adult participants may be the reason. Disappearing of BCG scar due to reduce the immune response over time is another explanation.

In this study, 16.5% of children and 19.7% of adults had reactivity of ≥10 mm. Our results demonstrate that a TST applied after BCG vaccination usually produces a reaction of <10 mm. These findings are consistent with reports from other countries with same TB prevalence.[12, 20, 21] A tuberculin survey in 2006 among school-aged children in a southern province of Iran detected a low positive TST rate (2.2%) (Alavi S M).[22] The observed low rate in Alavi's study may be due to inappropriate administration and poor storage of the PPD material resulted from large sample size and environmental factors (such as warm climate). Also, despite WHO efforts to standardize BCG vaccination[23] considerable microbiologic and genetic differences still exist among BCG strains.[24] These differences could account for numerous variations in immunogenicity.

Although correlation between age and TST positivity has been reported[25], in our study the occurrence of positive TST in adults was not significantly higher than children (19.7% vs. 16.5%). The post hoc power analysis showed that our sample size was not enough that the difference to be detected significant.

Comparison of TST results in scar positive and scar negative participants indicated that there is a significant relationship between the tuberculin reactivity and presence of BCG scar among children and adult groups. A potential source of observed difference is booster effect. Immunological memory created from a primary response to a specific pathogen, provides an enhanced response to secondary encounters with that same specific antigen. It is well established that T lymphocytes with specificity for a particular organism can persist in the host for many years after elimination organism (antigen-specific memory).[26] We assumed that PPD was capable of recalling memory T cells directed towards various epitopes of PPD shared with M. tuberculosis and scar formation was due to the stronger responses of cell-mediated immune system to BCG vaccine and thereupon scar positive participants have better reaction to PPD material than scar negative participants.

In addition, we examined the relationships between household crowding indicators and TST results. In our study, TST positivity was significant direct association with large family size and inverse association with living area space, number of living rooms, and family density. These results are in agreement with other reports.[27-29] These studies have shown that the risk of becoming infected with MTB is largely determined by the frequency and duration of exposure to airborne droplet nuclei in poorly ventilated indoor settings. Although in our study, proportion of TST posivity due to BCG vaccination is uncertain, but we assumed that some of the observed TST positivity resulted from latent TB or other non TB mycobacteria infection. Also, we examined the relationships between poverty and TST results. For estimation of poverty, we obtained the participants' income amount by their statements but

no significant association was found between TST positivity and the median household income.

Limitations: we have not recorded history of BCG immunization in a number of adult participants to compare them. Another limitation was lack of comprehensive income information to obtain because of limited access to other income data in the community.

References:

1.http://www.who.int/mediacentre/factsheets/fs104/en/ March 2010.

2. WHO, Global Tuberculosis Control: Surveillance, Planning, Financing. WHO report 2008; World Health Organization, Geneva.

3. Dodd PJ, Millington KA, Ghani AC, Mutsvangwa J, Butterworth AE, Lalvani A,.Corbett EL. Interpreting tuberculin skin tests in a population with a high prevalence of HIV, tuberculosis, and nonspecific tuberculin sensitivity. Am J Epidemiol 2010; 171: 1037-1045.

4. Gopi1 PG., Subramani1 R., Kolappan C., Venkatesh Prasad V, Narayanan PR. Estimation of annual risk of tuberculosis infection among children irrespective of BCG scar in the south zone of india. Indian J Tuberc 2006; 53:7-11.

5. Expanded Programme on Immunization. Programme review. Wkly Epidemiol Rec. 1994; 69: 87–90.

6. Bloom B. Tuberculosis: Pathogenesis, Protection, and Control. Washington, DC: American Society for Microbiology; 1994.

7. Hatami H. epidemiology and control of tuberculosis. in: Hatami H, Razavi S.M, Eftekhar A.H, Majlesi F, Sayed Nozadi M, Parizadeh S.M.J; Text book of public health Tehran: Ministry of Health. Second Edition 2006; 1121-1139.

8. Jasmer RM, Nahid P, Hopewell PC. Clinical practice. Latent tuberculosis infection. N Engl J Med 2002; 347: 1860–66.

9. Baker M, Das D, Venugopal K, Howden-Chapman P. Tuberculosis associated with household crowding in a developed country, University of Otago, Wellington, New Zealand Journal of Epidemiology and Community Health by the BMJ Publishing Group Ltd 2008; 62: 715-721.

10. http://www.cdc.gov/tb/publications/LTBI/appendixC.htm (accessed 18 August 2009).

11. Dean AG, Sullivan KM, Soe MM. OpenEpi: Open Source Epidemiologic Statistics for Public Health. Version 2.3. www.OpenEpi.com. Atlanta: Rollins School of Public Health, Emory University; 2009.

12. Sadeghi Hasanabadi A, Hadi N, Yaghoot M.Tuberculin reaction and BCG scar in children vaccinated at birth. Eastern Mediterranean Health Journal 1998; 4(1): 21-26.

13. Grindulis H, Baynham M, Scott P, Thompson R, Wharton B. Tuberculin response two years after BCG vaccination at birth. Arch Dis Child. 1984; 59: 614–619.

14. Hadfield JW, Allan J, Windebank W. Sensitivity of neonates to tuberculin after BCG vaccination at birth. Br Med J. 1986; 292: 990–991.

15. Shanmugalakshmi S., Dheenadhayalan V., Muthuveeralakshmi P., Arivarignan G., Pitchappan R.M. Mycobacterium bovis BCG scar status and HLA class II alleles influence Purified Protein Derivative-specific T-Cell receptor Vß expression in pulmonary tuberculosis patients from southern India. Infection and Immunity 2003, 71 (8): 4544-4553

16. Rani SH, Vijayalakshni V, Sunil K, Lakshmi KA, Suman LG, Murthy KJ. Cell mediated immunity in children with scar-failure following BCG vaccination. Indian Pediatr. 1998; 35: 123–127.

17. Sedaghatian MR, Kardouni K. Tuberculin response in preterm infants after BCG vaccination at birth. Arch Dis Child. 1993; 69: 309–311.

18. Santiago EM., Lawson E, Gillenwater K, Kalangi S, Lescano AG., Quella GD, Cummings K, Cabrera L, Torres C, Gilman RH. A prospective study of Bacillus Calmette-Guérin scar formation and tuberculin skin test reactivity in infants in lima, peru. pediatrics 2003; 112 (4): e298- e302 Available from: http://www.pediatrics.org/cgi/content/full/112/4/e298.

19. Grindulis H et al. Tuberculin response 2 years after BCG vaccination at birth. Archives of disease in childhood, 1984, 59: 614-9.

20. Sleiman R, Al-Tannir M, Dakdouki G, Ziade F, Assi NA, Rajab M. Interpretation of the tuberculin skin test in bacille Calmette—Gue´rin vaccinated and nonvaccinated school children. Pediatr Infect Dis J 2007; 26: 134—8.

21. Escobar AL, Coimbra Jr CE, Camacho LA, Santos RV. Tuberculin reactivity and tuberculosis epidemiology in the Pakaanova (Wari) Indians of Rondonia, southwestern Brazilian Amazon. Int Tuberc Lung Dis 2004; 8: 45—51.

22. Alavi S M, Sefidgaran G H, Tuberculin survey among school-aged children in Ahvaz, Iran, 2006. International Society for Infectious Diseases. Published by Elsevier Ltd. 2007.

23. Mallol J, Girardi G, Quezada A, Montenegro C, Espinoza P. Tuberculin reaction in healthy infants vaccinated with BCG at birth. Rev Chil Pediatr. 1990; 61: 252–257.

24. Behr M, Small P. A historical and molecular phylogeny of BCG strains. Vaccine. 1999; 17: 915–922.

25. Salomon N, Perlman D. C, Friedmann P, Ziluck V, Des Jarlais D. C. Prevalence and risk factors for positive tuberculin skin tests among active drug users at a syringe exchange program, Int J Tuberc Lung Dis 2000; 4 (1): 47–54.

26. Fitzgerald D. and Haas D.W, Mycobacterium tuberculosis. In: G.L. Mandell, J.E. Bennett and R. Dolin, Editors, Principles and practice of infectious diseases (6th ed.), Elsevier Churchill Livingstone, Philadelphia 2005; 2852–2853.

27. Drucker, E., P. Alcabes, W. Bosworth, and B. Sckell. Childhood tuberculosis in the Bronx, New York. Lancet 1994; 343: 1482–1485.

28. Rathi SK, Akhtar S, Rahbar MH, Azam SI. Prevalence and risk factors associated with tuberculin skin test positivity among household contacts of smear-positive pulnionary tuberculosis cases in Umerkot, Pakistan. Int J Tuberc Lung Dis 2002; 6: 851 857.

29. World Health Organization: Guidelines for Healthy Housing. Health Series 31.WHO: Regional Office for Europe 1988